RESPONSE UNDER 37 CFR 1.116
EXPEDITED PROCEDURE
EXAMINING GROUP 1643

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: CLASSEN, John B.	)	Art Unit: 1643
Serial No.: 08/591,651	)	Examiner: BRUMBACK, E.
	)	Washington, D.C.
Filed: February 12, 1996	)	May 1, 2000
For: METHOD AND COMPOSITION FOR AN EARLY VACCINE...	)	Docket No.: CLASSEN

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PATENT & TRADEMARK OFFICE

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APPELLANT'S BRIEF UNDER 37 CFR §1.192

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

S i r :

In response to the final rejection mailed May 4, 1999, please enter the following appellant's brief.

The notice of appeal was filed November 4, 1999.

The small entity fee of $150.00 for this appeal brief is enclosed (check no. 25700). Please charge any deficiency to deposit account 02-4035.

1. FORMAL MATTERS

1.1. REAL PARTY IN INTEREST

The real party in interest is Classen Immunotherapies.

1.2. RELATED APPEALS AND INTERFERENCES

There are no related appeals and interferences.

1.3. STATUS OF CLAIMS

Claims 5, 6, 8, 10, 11, 15, 16, 19, 26-30, 32-41, 43, 44, 46, 48-52 and 55-101 are pending.

1.4. STATUS OF AMENDMENTS

The following amendments were filed after final rejection (status "entered"/"not entered" indicated in parentheses):

June 14, 1999 Request to Withdraw Finality (entered, but request denied);

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September 7, 1999 Amendment After Final Rejection (entered); and
September 7, 1999 Supplemental Amendment After Final Rejection (not entered);
October 27, 1999 Response to Advisory Action and Renewed Request to Withdraw Finality (entered, but request denied); and
May 1, 2000 Substitute Supplemental Amendment After Final Rejection (filed, not yet considered).

2. SUMMARY OF THE INVENTION

Applicant has discovered that the timing of immunization with an immunogen, typically against an infectious disease, can affect the incidence or severity of a chronic immune-mediated disorder. Early immunization, typically prior to 42 days of age, appears to decrease the incidence or severity. See page 15, lines 2-10. Contrariwise, conventional pediatric immunization protocols, typically beginning at 6-8 weeks, actually can increase the probability that a mammal will develop a chronic immune-mediated disorder. See page 20, lines 11-15.

Applicant has already received a patent (5,728,385), issued on the parent application, for methods of reducing the incidence or severity of diabetes mellitis or systemic lupus erythrematosis by first administering an immunogen when the mammal is less than 42 days old (certain immunization schedules were excluded to avoid inherent anticipation).

Applicants have also received a patent (5,723,283) on a related application (a division of the corresponding PCT application) relating to methods of determining whether an immunization schedule affects the incidence or severity of a chronic immune-mediated disorder.

The instant claims are (1) additional therapeutic method claims, and (2) claims to kits for carrying out the desired immunization protocols.

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3. ISSUES PRESENTED

I. In the case of the kit claims, as rejected as anticipated by Madore (§7), Dengrove (§8), Halsey (§9), John (§10) and Onazono (§11), did the Examiner properly disregard the "labeling" limitation; more particularly, is there a "functional relationship" between the "labelling" ("printed matter") and the drug and its container ("substrate")?

II. Is "substantially reduces the incidence or severity" (claims 56, 59, 36, 33, 32, 27) indefinite (OA §5c)?

III. Is "substantially greater" (claim 6) indefinite (OA §5a)?

IV. Is "immunogen" or "immunogen other than BCG" indefinite (OA §5d)?

V. Is "specific times after birth" indefinite (OA §5e)?[1]

VI. Do the March 25, 1999 amendments to claim 32 violate the "description" requirement of 35 USC §112 para. 1?

VII. Is the specification enabling for the use of early immunization other than with a combined anthrax + DPT (or DT) composition, to reduce the incidence or severity of diabetes?

VIII. Is the specification enabling for the use of early immunization to reduce the incidence or severity of diabetes in a mammal other than NOD mice or BB rats, in particular, in a human?

IX. Is the specification enabling for the use of early immunization to immunize against an infectious disease as well as to reduce the incidence or severity of diabetes?

X. Is the specification enabling for the use of early immunization to reduce the incidence or severity of a chronic immune-mediated disorder, in particular, of an autoimmune disease (especially SLE), other than diabetes?

XI. Is the specification enabling for determining the

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[1] This rejection has been maintained, see Advisory Action of September 29, 1999, Sec. 8, but it is unclear to which claim it is still applied, in view of the entered amendment to claims 32 and 56.

effect of particular immunization schedules on the incidence or severity of immune disorders?

4. GROUPING OF CLAIMS

4.1. With respect to the rejection of the kit claims as anticipated by one or more references (issue I) the claims should be grouped as follows:

group I-A: claim 27 and all claims dependent thereon

group I-B: claim 59 and all claims dependent thereon

The basis for this grouping is the difference in the labeling limitation between claims 27 and 59.

4.2. With respect to the indefiniteness issues II and III, these are addressed to specific claims, and no further grouping is needed.

4.3. With respect to indefiniteness issue IV, the claims should be grouped as follows:

group IV-A: all rejected claims not listed in group IV-B

group IV-B: claims 5, 30, 55, 66-77

The basis for this grouping is that the claims of IV-B require particular immunogens.

4.4. Issue V is believed to be moot, although not formally withdrawn.

4.5. Issue VI applies only to claims 32, 6 and 101.

4.6. For issue VII the grouping is as follows:

group VII-A all claims not listed in VII-B or C

group VII-B claims 5, 30, 55, 66-77, 91, 93-95

group VII-C claim 92

The grouping is on the basis of whether all immunogens are recited (A) or not (B, C). Group C is specific to bacterial immunogens.

4.7. For issue VIII, the grouping is as follows:

group VIII-A all rejected claims not listed in other groups

group VIII-B claims 16, 43, 44, 46 (human)

group VIII-C claim 48 (animal model)

The grouping is on the basis of the subject to which the immunogen is administered.

4.8. For issue IX, the grouping is as follows:

group IX-A: claim 27 and all claims dependent thereon except 36; claims 32, 6, 56-58

group IX-B: claim 101

group IX-C: claims 36; claim 59 and all claims dependent thereon except 72-77.

group IX-D claims 72-73

group IX-E claims 74-77

The claims of group IX-A do not require immunization against an infectious disease. Group IX-B requires that at least one immunogen elicit an immune response which recognizes an immunogen associated with an infectious disease to which said mammal is susceptible, but not that this response be protective against the infectious disease. The group IX-C, -D and -E claims do require such protection. However, they are further differentiated in that the group IX-D claims name specific pediatric immunogens, and IX-E, specific nonpediatric immunogens.

4.9. For issue X, the grouping is as follows:

group X-A all rejected claims, not in other groups

group X-B 26, 48, 84 (diabetes)

group X-C 35, 48, 85 (SLE)

group X-D 79,34 (autoimmune disease)

The grouping is on the basis of whether the claim covers any chronic immune-mediated disorder (A) or a subset (B, C, D) thereof.

10. For issue XI, the grouping is as follows:

group XI-A all rejected claims not in other groups

group XI-B claims 8, 10, 11, 39, 40, 41, 50, 51, 52, 57, 58

The grouping is on the basis of whether the claim further limits the immunization schedule (B), e.g., by time of first

dose, number of doses, or interval between doses, or not (A).

PRIOR ART ISSUES

5.1. (Issue I). In the case of the kit claims, as rejected as anticipated by Madore (§7), Dengrove (§8), Halsey (§9), John (§10) and Onazono (§11), did the Examiner properly disregard the "labeling" limitation; more particularly, is there a "functional relationship" between the "labelling" ("printed matter") and the drug and its container ("substrate").

While, in a claim to a product, language of intended use is ignored, these kit claims require the presence of certain labeling. This is a tangible requirement, not a mere statement of intended use.

The labeling is what the PTO calls "printed matter". Printed matter may constitute an element of a patentable claim and be given patentable weight, if there is a sufficient functional relationship between the printed matter and its substrate. See In re Gulack, 217 USPQ 401 (Fed. Cir. 1983); In re Miller, 164 USPQ 46 (CCPA 1969). Here, the printed matter explains how to use the substrate (the immunogen) to achieve the desired result (reduction in the incidence or severity of a chronic immune-mediated disorder).[2]

The Examiner maintains the rejection of the kit claims as

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[2] The "printed matter" doctrine is closely allied with the old "mental steps" and later "mathematical algorithm" doctrines, and, in this regard, it is interesting to note that an invention applying the rules and instructions for a game ("Cricket") to an otherwise old dart machine was held to be potentially patentable because the algorithm was not a mathematical one. See Arachnid Inc. v. Medalist Mktg. Corp., 18 USPQ2d 1941 (W.D. Wash. 1991). The claimed instructions for use do not define a mathematical algorithm.

anticipated by Madore (§7), Dengrove (§8), Halsey (§9), John (§10) and Onazono (§11) on the ground that there allegedly is not functional relationship between the printed matter and its substrate, as required by In re Gulack, 217 USPQ 401 (Fed. Cir. 1983) and In re Muller, 164 USPQ 46 (CCPA 1969).

What is a "functional relationship"? Presumably, it implies that without the printed matter, the substrate would be **less capable** of performing its function.

In the case of In re Miller, claim 10 read as follows:

> A measuring device comprising: a spoon for measuring ingredients; and volume measuring indicia defined in a normal volumetric unit on said spoon of a selected ratio to but indicating a volume different from the actual volume of ingredients being added to and measured in said spoon by said indicia, and a legend attached to said spoon specifying said ratio.

The court's opinion reproduces two apparatus of this type. In Fig. 2, we see a measuring cup with the legend "ONE HALF RECIPE", and various volumetric indicia. The line marked "2 CUPS" actually corresponds to a volume of one cup, so, if a full recipe called for "2 cups", by filling to the line in question, one would actually be adding the amount appropriate for a half recipe. In Fig. 3, we see a set of measuring spoons with a "½ recipe" tag. Here, the spoon marked "1 teaspoon" has a true capacity of ½ teaspoon.

Were these indicia and legends to be removed, one would have cups and spoons worthless for accurate measurement. If just the legends were removed, one would have just a conventional looking (but inaccurate) measuring device or cup. The Court found that there was "a new and unobvious functional relationship between a measuring receptacle, volumetric indicia thereon indicating volume in a certain ratio to actual volume, and a legend indicating the ratio".

Similarly, in the instant kit claims, there is a new and unobvious relationship among "containers holding

pharmaceutically acceptable doses of one or more immunogens" (which is like Miller's "receptacle") the "labeling" of the containers to indicate the identity and amount of each immunogen they contain (which is like Miller's "volumetric indicia")[3] and the "instructions" for use (which is like Miller's "legend").

The last of these points deserves particular emphasis. Miller's "legend" is an instruction for use. "One Half Recipe" is an instruction to the cook to use the cup or spoon se tin question when he or she wishes to prepare a "one half" recipe without recomputation of the required amount of each ingredient. Without the cook to interpret the legends and indicia, the cup and spoons do not perform any function. Their functionality resides in what they communicate to the cook. They do not help the receptacle hold more ingredients, or keep them fresher. They do not make the receptacle more watertight or airtight. Their relationship -- especially the legend's relationship -- to the receptacle is closely akin to the relationship exhibited by the printed matter in the instant kit claims to the immunogens of those claims.

In Gulack, the claim was to an educational device, which could take the form of a hat with a headband. Imprinted on the headband (the substrate) was a cyclic sequence of integers (the printed matter) obeying a particular mathematical rule. What was the functional relationship? According to the CCPA, the digits -- the printed matter -- were "related to the band in two ways: (1) the band supports the digits; and (2) there is an endless sequence of digits... exploit[ing] the endless nature of the band". In contrast, in the prior art Wittcoff reference, there was printed matter on the band, as in (1) above, but the data items were independent rather than arranged in a particular sequence.

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[3] While this is not explicit in claims 27 and 29, it is an FDA requirement. The Supplemental Amendment, if entered, would make this explicit.

Here, the labeling establishes a sequence, albeit temporal rather than spatial, for the use of the immunogens of the kit. Bear in mind that this relationship is between the printed matter and the immunogens, which are a part of the overall "substrate". In Gulack, the distinguishing relationship was between one printed element and another printed element. Hence, the present case actually presents a stronger justification for the finding of a functional relationship than does Gulack.

While the immunogens are functional despite the labeling, that does not mean that a functional relationship is absent. Congress, in enacting the Food, Drug and Cosmetic Act (FDCA), recognized the existence of a functional relationship between a drug and its labeling. Thus, a new drug is not approved per se, rather it is approved for a particular indication (use). The new drug application includes "specimens of the labeling proposed to be used for such drug", see FDCA Sec. 505(b)1)(F). The FDA reviews the NDA and can refuse to approve if the testing was inadequate to show that "such drug is safe for use under the conditions prescribed, recommended or suggested in the proposed labeling thereof" (see FDCA Sec. 505(d)(1)) or the results "show that such drug is unsafe for use" or "do not show that such drug is safe for use" under "such conditions" (see FDCA Sec. 505(d)(2)). Moreover, approval may be refused if "such labeling is false or misleading in any particular" (see FDCA Sec. 505(d)(7)).

Once a new drug has been approved, that approval may be withdrawn for the same reasons that approval could have been withheld in the first place. See FDCA Sec. 505(e).

Moreover, the FDCA draws a distinction, for all drugs, between adulteration and misbranding. If a drug contains a substance which is deletenous to health, it is adulterated. See FDCA Sec. 501. However, even a drug free of deletenous substances can be sanctioned if it is misbranded. A drug is misbranded if "its labeling is false and misleading in any

particular", see FDCA Sec. 502(a). More significantly, it is misbranded "unless its labeling bears (1) adequate directions for use; and (2) such adequate warning against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application." See FDCA Sec. 502(f). A possible loophole is closed by FDCA Sec. 502(j), which says that a drug is "misbranded" if it is "dangerous to health when used in the dosage manner, or with the frequency or duration prescribed, recommended or suggested in the labeling thereof."

Prescription drugs dispensed by filling the prescription of a physician are exempt from Sec 505(f) and (j), cited above, but only if the drug bears a label presenting "the directions for use and cautionary statement, if any, contained in such prescription." FDCA Sec. 503(b)(2)

While a physician may prescribe a drug for an off-label use without violating the FDCA, such prescription may be considered medical malpractice, and insurers may refuse to pay for such use.

We caution the Examiner against an overly restrictive definition of a "functional relationship", namely, that "without the printed indicia or numbers, the substrates lose their function." The case law does not justify that definition.

In Gulack the substrate was a headband. It remained functional as a headband, only its educational function would have been lost if the integer sequence were omitted. In Miller, the substrate was a measuring cup or spoon. It could still be used as a cup or spoon if the indicia were omitted. Thus, it is clear that neither case presented a substrate whose function was totally dependent on the indicia.

Here, it is true that the immunogen (if protective in its own right) could be used to protect against the corresponding infectious disease. However, without the claimed directions

for use, the clinician would not know how to use it to limit the increased incidence or severity of the disorder attributable to late immunization.

In determining the functionality of an immunogen, it is appropriate to consider its side effects, not just its specific immunogen effect. If the side effects are detrimental, its functionality is reduced. If the side effects are beneficial, its functionality is enhanced.

The fact the immunogen has a residual level of functionality, absent the indicia, does not mean that there is no functional relationship between the immunogen and the indicia (labeling). If the latter increases the functionality of the immunogen, the necessary relationship exists and it is proper to give patentable weight to the labeling limitation.

An interpretation of "functional relationship" as meaning necessary for the functioning of the substrate is inconsistent with the alternative holding of the Federal Circuit in In re Lowry, 32 USPQ 2d 1031 (Fed. Cir. 1994). Lowry claimed memory for storing data which comprised a particular data structure (a pyramidal and hierarchical arrangement of "attribute data objects", ADOs), a data processing system comprising a database, a CPU, and memory means for holding the claimed data structure and methods of manipulating ADOs. The Examiner rejected the memory claim under ' 101, the system claims as obvious, and the method claims as anticipated. The Board reversed the ' 101 rejection, and upheld the prior art rejections. According to the Board, Lowry's data structures were analogous to "printed matter" and lacked a "functional relationship" to the substrate (the memory).

On appeal, the Federal Circuit held that because Lowry's data structures upon storage in memory, cause electromagnetic changes, there is a physical change, albeit invisible to the eye, and hence the data structures are not analogous to "printed matter".

However, it continued that even assuming that the analogy

is valid, the Board erred in its reliance on Gulack. It pointed out that the ADOs enabled "more efficient data processing operations on stored data" in particular, that they "facilitate addition, deletion and modification of information stored in memory". The memory, of course, has a "function" even without Lowry's data structure. Lowry's merely structures "provided increased efficiency". However, that qualified as a "functional relationship": "In sum, the ADOs perform a function, Gulack requires no more".

We also think it worth reiterating that if the labeling is given patentable weight (as we think proper as a matter of law), it is clear that the claims are not anticipated or rendered obvious by the reference. While it is certainly normal for an immunogen to be labeled with directions for use, to immunize against an infectious disease, and with warnings of side effects like acute toxicity, applicant was the first to teach that it should be labeled to direct its administration so as to limit the increased incidence and severity of a chronic immune mediated disorder (e.g. diabetes).

Consistent with this analysis, the PTO has allowed claims with "labeling" limitations.

Gerbe, USP 3,627,122, SYSTEM AND APPARATUS FOR THE ADMINISTRATION OF DRUGS (1971), claims an apparatus comprising compartmented trays, with "a patient and dose identification card" covering the bottom of each compartment, the card "having a folded portion...for holding said card in place". The claim also recites that each compartment has "a longitudinal pocket in one wall for a signal identification card".

Phykitt, USP 5,687,841, COMBINATION SHIPPING CONTAINER, MIXING AND DRINKING VESSEL (1997) claims the combination of analgesic medications and a package which serves both a shipping container and a mixing vessel. Claims 21-22 recite

> 21. The combination, according to claim

> 1, wherein said package further includes at least one of indications, directions, warnings, drug interaction precautions, active ingredients information and storage information disposed on an outer surface of one of said back portion and said front portion of said package.
>
> 22. The combination, according to claim 21, wherein said package includes each of said indications, said directions, said warnings, said drug interaction precautions, said active ingredients information and said storage information disposed on said outer portion of said back portion of said package.

Robertson, USP 5,752,723, PHARMACY LABEL AND PRESCRIPTION DRUG DISPENSING (1988) claims (18) "a labeled prescription drug package comprising...indicia comprising the name of a prescription drug, the dosage for proper administration of the drug, and the quantity of the drug to be provided in a package, imaged on said first label section".

See also Olney, USP 5,011,853 (claim 18= "a label which indicates that said pharmaceutical agent can be used for reducing the neurotoxicity of at least one cholinergic neurotoxin"); Kelly, USP 5,208,031 (claim 4= "the packaging material indicates that the sexual lubricant mixture... can reduce the risk of being infected by at least one type of sexually transmitted virus"); Sanders USP 4,820,635 (claim 1= "A kit ...comprising... instructions for performing the assay").

This is the first of several points in the brief in which we cite prior patents as evidence that a particular claim is acceptable. while we agree with the PTO that such evidence is not conclusive -- it certainly could not justify a legal position which was plainly contrary to the patent statute -- we cannot agree that is legally irrelevant. The courts have repeatedly found such evidence to be probative. Of course, the greater the number of patents cited, the more weight they carry. And the examiner is welcome to attempt to rebut the

evidence of showing that a difference in the disclosure justified the difference in prosecution. However, the examiner cannot simply ignore the evidence.

The following cases illustrate the relevance of prior patents:

Ex parte Brian, 118 USPQ 242, 245, (POBA 1958) (past practice of office in accepting definiteness of "fingerprint" claims);

In re Chakrabary, 596 F.2d 952, 985-86 (CCPA 1979) (product claims reciting microorganisms previously treated as directed to statutory subject matter);

Andrew Corp. v. Gabriel Electronics, Inc., 6 USPQ 2010, 2012 (Fed. Cir. 1988) (term "substantially" is "ubiquitous" in patent claims and therefore considered definite);

In re Cortright, 49 USPQ2d 1464 (Fed. Cir. 1999) (Construction of "restore hair growth" for purpose of determining both §112 enablement and §101 utility; prior art references may be indicative of how a claim term will be interpreted by those of ordinary skill in the art);

Vitronics Corp. v. Conceptronic Inc., 39 USPQ2d 1573, 1578-9 (Fed. Cir. 1996) (prior art used to demonstrate how a disputed term is used by those skilled in the art, and indeed is more objective and reliable than post-litigation expert opinion testimony);

Pioneer Hi-Bred International v. J.E.M. Ag Supply Inc., 49 USPQ2d 1813, 1819 (N.D. Iowa 1998) (issuance of Boehm USP 2,048,056 in 1936 is evidence that "in those instances where inventors showed they could define a reproducible plant meeting the limits of §112, plant patents were issued under §101".)

The purpose of the patent system is to encourage innovation. The claims are a means of defining the invention

in such a manner that it is reasonably clear what has been patented. It is one thing to reject a claim because it covers subject matter which is disclosed or suggested by the prior art, or which is not enabled. It is quite another to reject it on what amounts to stylistic grounds.

The PTO and the courts have recognized the propriety of once exotic claim formats-- "Jepson" claims, "Markush" claims, "product-by-process" claims, "fingerprint" claims, and claims with "negative", "functional", or "alternative' limitations -- because they have realized that public policy demands that inventors not be hindered by hypertechnical claim drafting rules from fully protecting novel, nonobvious, and adequately disclosed inventions.

The instant "kit" claims are a case in point. Applicant has discovered that immunization can --depending on timing - either increase or decrease the incidence or severity of chronic immune-mediated disorders such as diabetes and SLE. A traditional product claim does not sufficiently protect applicant, as it cannot cover a prior art vaccine, even if that vaccine were used without consideration of its effect on a chronic immune-mediated disorder.

For a method claim to protect the invention, it must be crafted to avoid any instance in which the prior art use of a vaccine to immunize against an infectious disease might inherently (although inadvertently) have had the effect of also reducing the incidence or severity of a chronic immune-mediated disorder, as otherwise it could be held invalid on the ground of "inherent anticipation". Applicant has studied the literature, and has attempted to phrase the claim so as to avoid inherent anticipation, but simply cannot be sure that all such art has been avoided. An early immunization protocol might be set forth in an old or obscure journal anywhere in the world, or might have been used "publicly", without formal publication, in the United States. Indeed, the specification at page 31, lines 9-18 expressly recognizes the problem:

> The inventor appreciates that it is conceivable that a prior experimenter has, without recognition of its anti-chronic immune-mediated disorder activity, proposed or even practiced an immunization schedule which falls within the present disclosure, If, under the applicable law, such a proposal or practice would be deemed to anticipate or render obvious an invention here claimed, then it is within the inventor's contemplation to excise from the invention the specific embodiment in question, preserving to the maximum degree permitted by law the scope of protection originally sought.

A second problem with method claim protection is that it is geared to use of immunogens to decrease the incidence or severity of a chronic immune-mediated disorder. However, the Applicant has also enriched the art by teaching it to examine the chronic immune effects of conventional immunization. A vaccine manufacturer may find, after testing inspired by Applicant, that early immunization, while less likely to elicit this adverse effect, is also less effective against the infectious disease, and therefore continue to recommend, with appropriate warnings, late immunization. A "method of reducing the incidence or severity of a chronic immune-mediated disorder" claim would not reach this practice, even though the manufacturer would clearly have benefitted from Applicants's teachings.

A third problem is that the method claims are infringed by physicians. Applicant would prefer to assert direct infringement by the manufacturer. It is easier for Applicant to monitor vaccine labeling than to identify which doctors are following the claimed early immunization strategies.

A "kit" claim, like claims 27 and 59, solve these problems, without giving Applicant control of subject matter to which he is not entitled. Claim 27 and 59 are infringed only if the immunogen is distributed or sold with labeling either giving instructions which call upon the physician to practice the invention, or warnings indicating that the manufacturer has screened the immunogen as taught by Applicant.

Claims 27 and 59 could not be inherently anticipated by the naive use of the immunogen in an early immunization schedule, since such use, by definition, would make no reference to the effect of the immunogen on the incidence or severity of a chronic immune-mediated disorder.

6. DEFINITENESS ISSUES

6.1. (Issue II). Is "substantially reduces the incidence or severity" (claims 56, 59, 36, 33, 32, 27) indefinite (OA §5c)?

The use of the relative term "substantially" has been repeatedly upheld when a suitable standard, such as a stated purpose, or representative examples, are disclosed. Andrew Corp. v. Gabriel Electronics, Inc., 6 USPQ2d 2010, 2012 (Fed, Cir. 1988); Seattle Box Co., Inc. v. Industrial Crafting & Packaging, Inc., 221 USPQ 568 (Fed. Cir. 1985); In re Mattison, 184 USPQ 485 (CCPA 1975).

It is clear that a rejection in incidence of 50%-75% would be considered substantial, see page 55, lines 17-20. However, this is not the minimum acceptable reduction.

In Ex. 1, the incidence of diabetes was reduced from 65% at 28 weeks in NOD mice, to 57.9% for the plague vaccine group and 42.1% for the anthrax vaccine group. See page 82, lines 21-27. That is a reduction of 7.1 percentage points out of 65, or 10.9%, for the plague vaccine, and 22.9 percentage points out of 65, or 35.2%, for the anthrax vaccine.

In Ex. 4, an experiment was conducted with another diabetes model, BB rats. The rats given anthrax + DTP had a diabetes incidence of 35% at 32 weeks, as compared to 54% for control rats. This was, as noted in the spec., a 34% reduction in incidence. See page 87, lines 15-22.

Other reductions in incidence may be extracted from the other examples, experimental and epidemiological, but the above seems sufficient to establish a standard.

6.2. (Issue III). Is "substantially greater" (claim 6) indefinite (OA §5a)?

With regard to "total dosage... substantially greater than that required for immunization, "the Examiner asks "how much greater?" This is similar to the question asked by the Examiner in In re Mattison, 184 USPQ 485 (CCPA 1975) with respect to the meaning of "substantially increased efficiency":

> We are not persuaded by the board's reasoning that one skilled in the art would not be able to determine the scope of the claimed invention in terms of a specified percentage value. General guidelines are disclosed for a proper choice of the substituent Ep together with a representative number of examples.... Hypothesizing whether an increase in efficiency of 3%, 30%, or 300% is necessary for said increase to be classified as substantial is not determinative of the issue of whether the claims satisfy 35 U.S.C. 112, second paragraph.

The court reversed the rejection. Clearly, it is not necessary that all quantitative limitations of a claim be expressed as exact numbers.

Here, one may compare the total dosage under a schedule intended solely to immunize against a schedule intended solely to immunize against an infectious disease with the total dosage under a preferred schedule.

Three standard schedules, reflecting prior practice, are discussed on pages 31-32. Under these schedules. during the first 112 days (16 weeks) after birth, 3 administrations are given of each immunogen (D, T, P, polio, HepB, HiB). In the preferred schedules on pp. 107-108, schedule 3 called for five doses of HepB and six of DTP and Hib during the first 16 weeks. This clearly is considered a substantial increase in the total dosage. The preferred schedules, together with the stated purpose of the invention, provide a standard for

judgment.

6.3. (Issue IV). Is "immunogen" or "immunogen other than BCG" indefinite (OA §5d)?

There has been some question as to the basis for this rejection. Initially, the Examiner said that the claims "fail to positively set forth what is claimed" (October 2, 1998 action at page 7, lines 20-21).

In response, we stated that "other than BCG" is proper - one can disclaim a prior art species in a genus. Applicants were concerned with the early BCG vaccinations reported by Grange and Stanford, cited at page 6, lines 11-14, and an animal study by Harada, cited on page 9, line 16 to page 10, line 4. Excission of prior art is allowed by In re Johnson, 194 USPO 187 (CCPA 1977) and here supported also by page 31, lines 9-18 and page 99, line 22 to page 100, line 2.

The May 4, 1999 action declared, "For the exclusion to be proper, the other species of the genus must have been disclosed. In the instant case, one immunogen other than BCG" does not define the metes and bounds of the other immunogens".

A larger number of "other species" of immunogen are in fact disclosed, see, e.g., original claims 17, 19 and 30. "The metes and bounds" are as well defined as that of "immunogen" per se, because it is the genus ("immunogen") less a single species ("BCG").

Nor is "immunogen" per se indefinite. The term "immunogen" is formally defined at page 33, line 19 to page 34, line 2. Numerous examples are given on pages 35-36, and the term is widely used in the art. Also, the specification formally distinguishes immunosuppressants (defined at page 36, lines 16-18), tolerogens (defined at page 36, lines 20-23), immunocyte receptor ligands (page 37, lines 9-12), anti-receptor molecules (page 39, lines 12-21), transplanted cells (page 39, lines 22-29), and general immune modulators (page

40, lines 1-18).

6.4. (Issue V). Is "specific times after birth" indefinite (OA §5e)?[4]

So far as we are aware, the issue is moot in view of the entered amendment to claims 32 and 56. However, since the advisory action maintains this rejection, we must address it.

In brief, this phrase indicates that the doses are scheduled, not haphazard.

7. DESCRIPTION ISSUES

(Issue VI). Do the March 25, 1999 amendments to claim 32 violate the "description" requirement of 35 USC §112 para. 1?

Claims 6, 32 and 101 have been rejected (OA, Section 12) because the added limitations allegedly do not satisfy the description requirement, i.e., they were not part of the original conception of the rejection.

Claim 6 is rejected solely because it is now dependent on claim 32. The same appears to be true of claim 101, since it is not separately argued and the immune response it envisions would appear to be inherent in the immunization against an infectious disease contemplated by original claim 31. Hence, the rejection hinges on claim 32.

Claim 32 was amended to introduce the following limitations:

(1) if only one immunogen is administered, it is other than BCG;

(2) if the one immunogen is whole cell pertussis, the schedule is one other than a schedule of three doses at one week intervals, all given in the first month;

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[4] This rejection has been maintained, see Advisory Action of September 29, 1999, Sec. 8, but it is unclear to which claim it is still applied, in view of the entered amendment to claims 32 and 56.

and

(3) if all the immunogens administered are selected from a list of 10 immunogens, either

(a) one or more immunogens are administered on at least three different dates prior to 42 days after birth, or (b) one or more immunogens are administered on at least three different dates, and the maximum interval between administrations is about two weeks, or less.

Limitations (1) and (3) were copied from claim 1 of Classen, USP 5,728,385, which issued on the parent application, except that claim 32 refers to "one or more immunogens" instead of just "immunogens" to make it clear that a single immunogen could be administered. Note that the immunogens administered on different dates could be the same or different.

The Examiner says that because this case is a CIP of the prior case, and does not incorporate the prior case by reference, he cannot assume that just because there was descriptive basis in the parent case (as implied by the issuance of a patent) that there is descriptive basis here.

With regard to the "other than BCG" limitation (1), the limitation appears to be intended to excise prior art like that of Grange and Stanford (1990) cited at page 6, lines 11-14, and Harada (1990), cited at page 9, line 16 to page 10, line 4, and hence "described" by page 31, lines 9-18. Moreover, original PCT[5] claim 1 (which automatically has "description") recited "said one or more immunogens... optionally including at least one immunogen other than BCG". See also original PCT claims 5 ("other than BCG,... yellow

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[5] This application is the national stage of PCT/US94/08825. This PCT application originally presented 24 claims. In IPE, original claims 1, 3, 4, 7, 12, 13, 18, 23 and 24 were deleted, and 25-30 were added. On national stage entry, a preliminary amendment cancelled 20 and 22 and added 31-33.

fever", total of 21 immunogens listed) and claim 7 ("other than BCG...also...other than smallpox").

Turning to limitation 3(a), we have already explained the basis for at least three dosings prior to 42 days after birth (original claim 13). With regard to 3(b), the basis for at least three dosings (not necessarily all prior to age 42 days) is in original claim 9 and for a maximum interval of about two weeks, at original claim 11. The ten immunogens in question are BCG (from original claim 1) plus those listed in original PCT claim 4 (with the possibly inadvertent exception of hepatitis A). These are the ten pediatric immunogens listed on page 35, lines 24-26, and hence the ones for which the risk of inherent anticipation was greatest.

Limitation (2) was introduced to avoid any possibility of inherent anticipation by Adams (1947) (of record)[6], as cited in Table 5 of Halsey (of record). Excission of a prior art species from a generic claim is proper, see In re Johnson, 194 USPQ 187 (CCPA 1977) and indeed was contemplated as a possibility, see page 31, lines 9-18. The Halsey article is cited in the specification (p. 109) and incorporated by reference, as are all articles (including Adams) cited by Halsey. See pp. 99-100. Hence, there is no violation of the "description" requirement.

We would add that there is specific support for giving at least three doses (original claims 9, 12 and 13), for one week intervals (original claim 10), and for first administration at 7 days old (original claim 8)[7].

The Advisory Action of September 29, 1999, at page 8 raised the issue of whether Applicant could rely on the language of the original PCT claims. It is well established that the original claims of a U.S. application are a part of

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[6] Adams immunized with "phase I superconcentrate vaccine", with a total dose of "100,000,000,000 organisms".

[7] IPE claim 9 also supported "at least one immunogen other than pertussis".

the original description. See MPEP § 2163.03(I), citing In re Koller, 204 USPQ 702 (CCPA 1980).

The question is whether, when a PCT application is filed which designates the U.S., and the PCT claims are amended during IPE, whether the "original" claims for purpose of 35 USC § 112 include the PCT claims as filed.

We have two independent bases for urging that they are, at least in this case.

First, 35 USC § 363 clearly states "an international application designating the United States shall have the effect, from its international filing date under article 11 of the treaty, of a national application for patent regularly filed in the Patent and Trademark Office except as otherwise provided in section 102(e) of this title." Clearly § 102(e) has nothing to do with the "description" requirement, which is based on § 112. So the international application as filed, with claims 1, 7, 12 and 13, has the same effect as a U.S. application filed that day.

Secondly, the Examiner's attention is respectfully directed to section 16 of the transmittal letter, item 4

> "A courtesy copy of the International Preliminary Examination Report with annexes. Note: Please use the claims as they appear in the IPER annexes as the claims in this case. Claims indicated as "deleted" in the annex should be deemed presented on filing but cancelled herewith by preliminary amendment, to avoid renumbering."

Hence, the PTO was instructed to treat original PCT claims 1, 7, 12 and 13 as if they had been presented at the time of national stage entry, and then, a moment later, cancelled. The original claims of a U.S. application are part of the description even if they are subsequently cancelled.

8. ENABLEMENT ISSUES

8.1. Relationship to Prior Patents

At the outset, we would like to point out that the claims at issue are essentially parallel in scope to those granted in USP 5,728,385 and USP 5,728,283. These patents allowed claims which generically recited administering "immunogens" to "mammals". Those patents are presumptively valid under 35 USC §282. Moreover, the actions of the prior examiner in those cases is entitled to full faith and credit.

8.2. Summary of Office Actions

In the first office action, mailed October 2, 1998, the Examiner questioned whether the claims were enabled for subject matter other than just "immunizing against an infectious disease and against a chronic immune-mediated disorder in a mammal less than 96 months of age where the first dose begins within 42 days after birth wherein the immunogen is a combined anthrax vaccine and whole diphtheria, tetanus (i.e., DPT) composition"[8] (page 2, lines 14-18).

The wording of this passage implied that the rejection was not concerned with the choice of "mammal" (human v. mice v. rats) or the choice of "chronic immune-mediated disorder (diabetes v. other disorders). However, the body of the rejection questioned these choices, too.

In particular, the office action mailed October 2, 1998 argued that

(1) the art of preventing chronic immune-mediated disorders is a highly unpredictable [one, because]... the precise mechanisms by which the majority of autoimmune

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[8] "DPT" implies the presence of pertussis (P) immunogen, whereas "DT" is just diptheria and tetanus. The Examiner probably intended to recite "DT" since an anthrax + DT combination was administered in Exs. 2 and 3. However, those examples also looked at anthrax + DTP.

diseases remains unclear (page 2, lines 23-25)[9];

(2) the art considers the question of the earliest age at which to immunize [against an infectious disease] a difficult one to answer (OA page 3, lines 19-23)[10];

(3) there are no vaccines for a number of the infectious viral conditions encompassed by the claims and hence no enabling disclosure of how to vaccinate against those conditions (page 6, lines 4-6)[11];

(4) the specification was limited to a teaching of the antidiabetic effect of a combined anthrax/DPT vaccine in NOD mice, MRL mice,[12] and BB rats (OA page 5, lines 13-15);

(5) there is no way to calculate what dosage, method of administration, and frequency of administration is required to prevent, for instance, HIV, HCV and HSV infection, (OA page 6, lines 4-6 and 11-13);

(6) there is no way to calculate what dosage, method of administration and frequency of administration is required to prevent "immunizing with an immunogen in such amounts and at such times as would substantially induce an immune-mediated disorder" (page 6, lines 13-17); and

(7) there is a dearth of guidance with respect to chronic immune-mediated disorders other than diabetes.

The final action mailed May 4, 1999 considers the issue

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[9] Applicants do not purport to teach a method of "preventing" a chronic immune mediated disorder, only of reducing its incidence or severity.

[10] The question was whether to immunize later when the infants' immune system was more mature, but thereby running the risk that the infant would contract the disease in the interim.

[11] The Examiner mentions hepatitis C virus (HCV), HIV, herpes viruses (esp. HSV-1 and HSV-2), adenoviruses, papoviruses, parvoviruses, and flaviviruses.

[12] As explained in the specification at page 81, lines 2-28, the MRL mice are a model for systemic lupus erythrematosis (SLE), an autoimmune disease which is "genetically, immunologically and clinically very different from diabetes".

of enablement in subsections 4a-4j. The arguments in these subsections may be briefly characterized as follows (where more than one issue is addressed in a single subsection, I list the issues in separate paragraphs, e.g., "a1" and "a2"):

a1) applicant does not elucidate the significant differences between anthrax and DPT;

a2) applicant has not demonstrated the same effect for "viral immunogens absent bacterial proteins and liposaccharides that has been demonstrated for the described bacterial antigens";

b1) an alternative argument for the effectiveness of BCG is that it contains heat shock protein, a "known tolerogen";

b2) more generally, the epidemiological data presented is inconclusive;

c) because the mechanisms by which autoimmune disease arise is unknown, and their prevention is unpredictable, it is unclear whether the full breadth of the claimed invention would have a positive effect in treating autoimmune disease;

d) the relevance of the Classen declaration statement that only the pertussis and BCG vaccines have been shown to contain an immunogen that cross-reacts with an autoantigen associated with type I diabetes mellitus is not clear;

e) applicants' stated mechanism of action is only speculative;

f1) to the extent that applicants claim "a kit for use to protect a mammal against an infectious disease...", this suggests that the kit is used to elicit a [protective] immune response to the immunogen;

f2) it is unclear whether the mouse and rat data can be extrapolated to human infants because of the differences in growth and maturation rates;

g) autoimmune diseases are not known to share a common mechanism and hence would not have a common cure or palliative;

h) the two patents identified by applicants as pertinent to the number of examples required are legally irrelevant;

i) while the NOD mice and BB rats are accepted animal models for human diabetes, the extrapolation from rodents to humans is still in question because of the criticality of the age of administration of the immunogen and the difference in maturation rates between rodents and humans; and

j) it would require undue experimentation to determine effective immunization schedules for a vaccine against an infectious disease (HIV, HCV, HSV) for which a protective immunogen is not yet known (or, to put it another way, for which the known antigens are not immunogenic).

8.3. Evidence of Enablement/Operability

Before responding to the rejections in detail, we would like to lay out applicants' primary evidence of enablement/operability. The present specification presents five experimental examples, which are summarized below.

Example 1

Shows reduction in incidence of diabetes in NOD mice receiving (a) anthrax or (b) plague, on days 8, 15 and 29. The anthrax was more potent.

Example 2

Shows further reduction in incidence of diabetes in NOD mice receiving anthrax on days 1, 3, and 10, and weeks 4, 6, 8, 10, 12 and 14. Still further reductions obtained by combining the anthrax with tetanus and diphtheria, and even

more with pertussis also provided.

Also shows that first immunization of NOD mice with DTP at 8 weeks leads to higher incidence of diabetes.

Example 3

Mice were injected with cyclosporine to make them prove to developing autoimmunity, and then were immunized with (a) anthrax + diphtheria + tetanus (ADT) at days 10, 17, 31 and 45 and (b) anthrax + DTP at days 6-8, 14-16 and 27-29 (3 admin.). Both treatment groups exhibited decreased incidence of anti-(gastric antigen) autoantibodies, with the effect being greater for group (b).

Example 4

BB rats (another diabetes model) were immunized with anthrax + DTP at days 1, 4, 11, 25, 39, 53, 61, 75, 89 and 103. They showed decreased incidence of diabetes relative to control rats.

Example 5

MRL/MPJ-lpr mice were used as a model of SLE. The mice were injected with anthrax + acellular DTP at days 1, 3, and 10, and weeks 4, 6, 8, 10, 12 and 14. The incidence of glomerulonephritis (a symptom of SLE) was reduced by this immunization.

Additionally, epidemiological data is presented in Example 101 and Tables I-IV. Table I compares different countries, with different immunization plans, for the same time period (roughly 1980-1990), while the other tables look at the effect of temporal changes in immunization schemes in a single country. Table I examines the effect of pertussis and BCG immunizations in various countries; Table II shows changes in the incidence of diabetes in Finland, explained at pages 93-95 as attributable to use of Hemophilus influenza and MMR vaccines. Table III focuses on Allegheny County,

Pennsylvania, and the discussion at pages 95-97 correlates changes with usage of Hemophilus influenza, pertussis and mumps vaccines. Finally, Table IV is said at pages 97-99 to evidence a connection between smallpox immunizations and diabetes. The first immunization was given earlier at the time of a smallpox epidemic.

Post-Filing Evidence

Classen and Classen, Infect. Dis., 6:449-454 (1997) presents some additional data.

Their table 1 is new, and correlates the incidence of diabetes in Sweden with BCG and smallpox immunization practices.

Their table 2 corresponds to Table I of the application, and adds data for Sweden (1990) to group 1; Switzerland (1985-1987) to group 2; and Malta (1980-1987) to group 4. (It omitted the data for Sweden (1987) that had been given in group 4 of Table I of the application.) It also adds a group 5 ("H-influenzae, pertussis, BCG vaccination, 0-1 month and school-aged") with an entry for Finland (1988).

Their table 3 corresponds to Table II of the application, and adds 1990-1992 data for the 0-4 and 5-9 age groups.

Their table 4 is new, describing the incidence of diabetes in New Zealand, and relating it to a national hepatitis B immunization program.

Smallpox data appears in Classen, J.B., and Classen, D.C. "Immunization in the first month of life may explain decline in incidence of IDDM in the Netherlans" Autoimmunity 31:43-45 (1999).

Another piece of evidence is the declaration of Dr. Classen executed July 8, 1994 and filed the same day in Serial No. 08/104,529, now USP 5,728,385. Certain of the experiments which were enumerated in this declaration are explicitly part of this CIP. Thus, section 2 of the declaration is now Example 4, section 3.1 is now Example 101, and section 4 is now Example 5. However, sections 5-8 are still worthy of

study. Section 5 refers to a "table VI", attached to the declaration, and summarizing the types of vaccines affecting type I diabetes. This section addresses the issue of scope of immunogens and their mechanism of action. Section 6 relates to devising an immunization schedule; section 7, to selecting a dosage; and section 8, to immunological pathways.

There is also the Classen declaration filed September 7, 1999, and addressing hepatitis B virus immunization.

8.4. (Issue VII) Is the specification enabling for the use of early immunization other than with a combined anthrax + DPT (or DT) composition, to reduce the incidence or severity of diabetes?

The first enablement issue is whether applicant is properly limited to a single combined immunogen of example 2 (anthrax + DPT).

While that was applicant's best tested immunogenic composition, it was not the only immunogenic composition shown to favorably affect diabetes. Anthrax alone (42.1% vs. 65% control), plague (57.9% vs. 65%), and anthrax + DT (7.7% vs. 65%) immunizations all resulted in reduced incidence, although the reduction of incidence with anthrax + DTP was superior.

The effectiveness of other immunogens is also suggested by Applicant's epidemiological data (Example 101 and Classen, et al., Infect. Dis. 6:449-54 (1997)), from which Applicant reasonably inferred that early immunization with BCG and smallpox vaccines reduces the incidence of diabetes, and that late immunization with BCG, Hemophilus influenza, hepatitis B, meningococci polysaccharide, measles, mumps and rubella immunogens can increase diabetes. (The latter also implies that early immunization with the same immunogens would decrease diabetes.)

Extrapolation to other immunogens is proper for several reasons.

First of all, the agents we used (anthrax and DPT) are very different, so, if they both have this effect on

autoimmune disorders, other agents are likely to do so, too.

Secondly, we present a rational basis (lymphokine release) for expecting a general effect of this type (see pp. 15-16).

Thirdly, the unpredictability of the relationship between autoimmune disorders and microbial infections has nothing to do with our invention. We are not suppressing an autoimmune disorder by suppressing a specific causative infection. Our Examples show an effect in infection-free mice and rats.

These points are developed in more detail below.

The present invention is directed to methods of reducing the incidence of an autoimmune disease, by early and frequent administration of immunogens.

It can be seen from both the experimental studies and the epidemiological data that a variety of immunogens -- plague, anthrax, diphtheria, tetanus, pertussis, BCG, Hemophilus influenzae, hepatitis B, measles, mumps, rubella and smallpox -- can affect the development of diabetes, and that early administration of BCG, plague, anthrax, anthrax + DT, anthrax + DPT, hepatitis B and smallpox immunogens can reduce the incidence of diabetes.[13]

Table VI of the 1994 Classen Declaration (copy enclosed), filed in the parent case, compared the anthrax, plague, DT, pertussis, Hib, BCG, smallpox and MMR vaccines in terms of the nature of the vaccine. There are considerable differences. Only the pertussis and BCG vaccines have been shown to contain an immunogen that cross-reacts to an autoantigen associated with type I diabetes mellitus.

Under these circumstances, it is clear that the anti-diabetic response cannot be entirely immunogen-specific, as there is no common epitope in question which could be eliciting the response. A nonspecific immune response must play an important role.

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[13] The effect of early administration of the other immunogens noted is not yet known, but is readily determined.

At page 15, line 14 to page 16, line 8 of the specification, Dr. Classen declares

> Without intending to be bound by any theory, early administration of immunogens can cause the release of lymphokines that may accelerate the maturation of the immune system. The immunization may act in several ways including:
>
> A. Enhancing destruction of autoimmune prone cells in the thymus;
>
> B. Enhancing the flow of normal T-cells from the thymus;
>
> C. Causing peripheral elimination of autoreactive T-cells that have escaped the thymus;
>
> D. Causing the release of interferons which prevent infection with autoimmune causing viruses; and/or
>
> E. Causing migration of macrophages into the area of administration as in an injection site and away from an vital organ like the islet cells of the pancreas. The invading macrophages have the ability to act as antigen presenting cells and induce an autoimmune response against the vital tissue.
>
> In contrast, the late administration of an immunogen can cause the release of lymphokines which may act as growth factors enabling autoimmune inducing cells to grown.

Lymphokines (and other cytokines) are discussed in more detail at pages 37-39 of the specification. Interferon alpha is specifically mentioned at page 38, line 7. The mechanism by which immunization with a broad range of vaccines at birth prevents diabetes can be explained through the release of alpha interferon (or other lymphokines). Alpha interferon is an molecule made by macrophages when they are activated by an immunological challenge such as an infectious organism or vaccine. Alpha interferon is routinely used to treat patients with hepatitis and other viral infections because the molecule has strong and broad antiviral activity. Alpha interferon induced by immunization at birth can help prevent diabetes through the suppression of congenital or neonatal infections,

also called vertical infections. Studies from Sweden and Finland have indicated that 27% or more cases of insulin dependent diabetes are linked to a vertical infection with Coxsackie B virus. See Dahlquist, et al., Diabetologia, 38:1371-3 (1995); Hyoty, et al., Diabetes, 44:652-7 (1995). This data is consistent with early reports linking the development of insulin dependent diabetes to congenital rubella infections. Ginspberg-Gellner, et al., Diabetologia, 27:87-9 (1984). Inhibition of these infections through nonspecific mechanisms, in particular release of alpha interferon following immunization at birth, explains why early immunization is associated with a reduced risk for developing diabetes. This mechanism of action also explains why early immunization prevents diabetes in NOD mice since a congenital viral infection has been suggested as a cause of diabetes in the NOD mouse. Gaskins, et al., J. Clin. Invest., 90:2220-7 (1992); Suenaga, et al., Diabetes, 37:1722-6 (1988); Nakagawa, et al., Diabetologia, 35:614-18 (1992).

The late administration of alpha interferon to patients has been reported to cause insulin dependent diabetes. Alpha interferon and the alpha interferon inducer Poly I:C have been shown to induce diabetes in rodents as well, explaining why late immunization induces diabetes in rodents. The induction of diabetes by late immunization also can be explained through the release of alpha interferon. The mechanism by which alpha interferon can induce diabetes include damaging the islet cells and speeding up a smoldering subclinical autoimmune disease.

The ability of interferon to modulate diabetes by two pathways, prevention through inhibiting viral infections and induction through stimulating an autoimmune response, explains the importance of timing of first immunization.

Potential immunogens, which could elicit, if administered early in life, an anti-diabetic immune response, are discussed in great detail at pages 33-36, 41-44, in the Examples, and original claims 3, 17 and 19.

Methods of screening immunogens for suitability are discussed at length at pages 53-75, and are further exemplified by Examples 1 to 4 of the specification.

In view of the plethora of examples of potential immunogens, the diversity of the immunogens already known to affect diabetes, the plausibility of the proposed non-immunogen-specific mechanism (lymphokine release) by which the anti-diabetic effect is exerted, and the detailed presentation of the screening methodology, it is clear that one skilled in the art can, without undue experimentation, identify additional immunogens that can, by early administration, reduce the incidence of diabetes.

Therefore it does not appear that the disclosure is enabling only for the listed immunogens, as other immunogens would be expected to have an anti-autoimmune disease effect and to be identifiable without undue experimentation.

The Examiner states that the precise relationship between auto immune responses and certain microbial infections is difficult to establish. That may be so, but the present invention does not require that one understand how the autoimmune disease is caused, merely that one interrupt the development of the autoimmune response. And even if there are "multiple mechanisms of induction of anti-self-responses", and the present invention interferes with only one of them, such interference is still an advance in the control of autoimmune disease.

8.4.1. The Examiner states in section 4(a) of the office action of May 4, 1999 that

> Applicant argues that the specification is enabled for the broad scope of the claims because anthrax, plague and DT were shown to favorably affect diabetes and further argues that anthrax and DPT are very different. Applicant, however, does not elucidate what the significant differences are between anthrax and DPT (the examiner has assumed that "DT" is diphtheria/tetanus and that "DPT" is diphtheria/pertussis/tetanus). What the

> disclosure has shown is a reduction in the incidence of diabetes in a mouse model by administration of one or more of five bacterial immunogens (*Bacillus anthracis, Yersinia pestis, Corynebacterium diphtheriae, Bordetella pertussis, and Clostridium tetani*). This effect appears to be amplified when two or more of these antigens are administered together. The immunogens as claimed include a myriad of different viral antigens, as well as bacterial antigens. Applicant has not demonstrated the same effect for viral immunogens absent bacterial proteins and lipopolysaccharides that has been demonstrated for the described bacterial antigens.

The Examiner appears to assume that all of the bacterial vaccines mentioned contain LPS. Presumably, this is important because a viral coat would not contain LPS. However, at least the DT vaccine contains protein toxoids, without significant amounts of LPS, and hence is akin --in the sense that it presents just proteins to the immune system-- to a viral vaccine.

The immune system does not treat viral proteins any differently than it does bacterial proteins. That is why both viral and bacterial vaccines of at least partially proteinaceous character are known in the art.

It is not up to Applicant to elaborate upon the exact antigenic differences among plague, anthrax, diphtheria, pertussis and tetanus. It is up to the Examiner to prove, if he can, that these vaccines are so similar that Applicant's success with these vaccines is not properly extrapolated to vaccines based on other immunogens. Nonetheless, we wish to point out the separate classifications of the source organisms in the art:

anthrax (Bacillus anthracis)
plague (Yersina pestis)
diphtheria (Corynebacterium diphtheriae)
pertussis (Bordetella pertussis)
tetanus (Clostridium tetani)

Anthrax and tetanus are in the family Bacillaceae, but plague is in the family Enterobacteriaceae, while diphtheria is in the Actinomycetes. The affiliation of Bordetella is uncertain, but these bacteria are strictly aerobic coccobacilli.

It would therefore be reasonable to expect that the divergence in antigenic makeup among the exemplified immunogens is substantial, in which case generic coverage of immunogens --especially coupled with a functional limitation -- is justified.

Besides the variety of bacterial immunogens which have been shown to reduce the incidence of diabetes, several viral immunogens have also been shown to have this effect.

The efficacy of a smallpox vaccine, administered at birth, has been established by epidemiological evidence. See Spec., pages 97-99, and Classen, J.B., and Classen, D.C.: "Immunization in the first month of life may explain decline in incidence of IDDM in the Netherlands," Autoimmunity 31:43-45 (1999).

More recently, the applicant has shown that a hepatitis B virus vaccine, administered on days 3 and 28 from birth, significantly protected NOD mice from the development of diabetes (see Declaration filed September 7, 1999).

8.4.2. The Examiner discounts (OA §4(b)) the relevance of the BCG epidemiological data because BCG contains "a known tolerogen, heat shock protein".

The epidemiological data related to administration of a live BCG (a whole bacterium), rather than of a purified heat shock protein. The subject was thus immunized with thousands of different membrane and intracellular proteins native to BCG. One of these may well have been heat shock protein, but there were certainly many others. Regardless of whether heat shock protein was functioning as an immunogen or a tolerogen, at least some of the proteins of the administered BCG preparation must have been functioning as immunogens because the preparation was administered as a vaccine, i.e., to elicit

a specific immune response protective against tuberculosis.

Applicant discovered that it is the timing of the administration that determines whether an immunogen increases or decreases the risk of developing autoimmunity. Based on the epidemiological data in question, it appears that early administration of BCG reduces incidence of diabetes, while late administration increases it. See specification Table I on pp. 101-102, and page 91, lines 4-6 and 8-11.

8.4.3. With regard to the other epidemiological data, the Examiner considers it inconclusive for the reasons stated in section 4(b). However, the Examiner's objections apply to any epidemiological study, and In re Irons, 144 USPQ 351 (CCPA 1965) held that use of "historical controls" is acceptable. Moreover, the epidemiological data does not stand alone.

8.4.4. In OA §4(c), the Examiner argues that preventing autoimmune diseases is highly unpredictable.

Actually, the claims do not call for "prevention", rather, for reducing the incidence or severity.

It is well accepted that immune suppressants like corticosteriods can suppress most if not all autoimmune diseases. It is also accepted that immune stimulants like interferons can exacerbate almost all autoimmune diseases. The PDR gives specific contraindication not to give interferons to patients with autoimmune disease (PDR (1999) on Roferon). Vaccines induce interferons and would be expected to increase the risk of autoimmunity. Immune stimulation is a common pathway for exacerbating autoimmunity. A second common pathway for induction of autoimmune diseases is through vertical transmission of viruses. Interferon release following immune stimulation with vaccines would expect to prevent this (see below, and Classen, J.B., and Classen, D.C.: "Vertically transmitted enteroviruses and the benefits of neonatal immunization" Diabetes Care 22(10):1760 (1999)).

It follows from the general effects of immune suppressants and immune stimulants on autoimmune diseases that there are common mechanisms at work.

8.4.5. It appears from OA §4(d) that the Examiner overlooks (sec. 4(d)) the relevance of the Classen declaration. The antidiabetic effect is not a specific immune response to a diabetes-associated autoantigens, because, e.g., diphtheria and tetanus are not known to cross-react with such an antigen. If the effect is not a specific immune response, it is reasonable to expect that it can be achieved with many different antigens.

8.4.6. While we have not established a mode of action (OA sec. 3(e)), the existence and assertion of a plausible mode of action renders the asserted utility more believable, and hence is legally relevant.

9. (Issue VIII). Is the specification enabling for the use of early immunization to reduce the incidence or severity of diabetes in a mammal other than NOD mice or BB rats, in particular, in a human?

9.1. MPEP §2107.02(c) specifically states that "data generated using in vitro assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility". It is well settled that animal data (or even in vitro data) can establish the utility of a therapeutic method in humans if there is an accepted correlation between efficacy in the animal in question, and efficacy in humans. See In re Jolles, 206 USPQ 885 (CCPA 1980); Nelson v. Bowley, 206 USPQ 881 (CCPA 1980); Cross v. Iizuka, 224 USPQ 739 (Fed. Cir. 1985). The law does not requires that this correlation be perfect, merely that it give the researcher a reasonable expectation that a drug which does well in animal testing will be successful in humans.

The expectation exists here because:

(1) the specification establishes efficacy in NOD mice, and NOD mice are an accepted animal model of diabetes mellitus in humans;

(2) the method of the present invention was effective in a second species of animals, BB rats, which are likewise accepted as animal models of human diabetes mellitus; and

(3) the utility of the present invention in humans is made more believable by human epidemiological data.

It is now widely accepted by those skilled in the art that type I diabetes in humans responds similarly to immune intervention as does diabetes in NOD mice and BB rats. Diabetes in all three species is considered to be an autoimmune disease based on the presence of islet cell autoantibodies and strong genetic linkage between the development of diabetes and MHC genes (New England Journal of Medicine 314:1360-1368,1986; Diabetes Reviews 1:15-42,1993). Immunological events occurring in the first 2 months of life have been clearly shown to be responsible for the development of diabetes in NOD mice and BB rats. Similarly, recent human epidemiology data shows that immunological events occurring at birth have a profound effect on the development of human diabetes. These events include maternal fetal blood group incompatibility as well as exposure to rubella virus and nitrates at birth (Diabetes Reviews 1:15-42,1993; Diabetologia 35:671-765,1992).

The concept of diabetes in humans responding similarly to diabetes in NOD mice is widely accepted. This has been justified by therapeutic experience. Clinical trials have shown that type I diabetes in humans can be prevented by immunosuppressants like cyclosporine when administered to prediabetics or newly diagnosed diabetics (Diabetes Reviews 1:15-42,1993). Immunosuppressants have a similar effect on NOD mice and BB rats (Clinical and Investigative Medicine 10:488-495,1987). The NIH recently embarked on a trial of screening up to 80,000 children to initiate a program of treating prediabetics with insulin immunotherapy, after a small phase I trial in humans supported results developed in NOD mice (Lancet 341:927-928,1993).

By reason of these findings, the art has often recognized

the value of NOD mice and BB rats as models for diabetes in humans and has used these models to evaluate anti-diabetic therapies. The citations of Appendix 2 hereto illustrate the degree of acceptance these models have earned.

As described in the attached Declaration, diabetes prone BB rats were immunized according to the method disclosed in the specification in order to show that the method of immunization could prevent diabetes in other species beside NOD mice.

BB rats spontaneously develop diabetes at an early age as is the case in NOD mice and humans. Many of the findings present in human type I diabetics and in NOD mice are found in BB rats leading experts to believe diabetes in BB rats is also a autoimmune disorder. Insulitis develops in the pancreas of BB rats before the onset of diabetes while antibodies develop to islet cells and possibly to insulin. Diabetes can be prevented by neonatal thymectomy as well as administration during the prediabetic period of cyclosporine, anti-lymphocyte antibodies, or purified lymphokines like TNF. Genetic experiments show that diabetes is closely linked to the MHC class II genes in BB rat as it is in humans. Many older rats develop autoimmune thyroiditis that is casually related to the development of diabetes as occurs in humans.

BB rats have an immunologically distinct disease from the disease in NOD mice. Diabetes develops in approximately equal numbers of males and females in contrast to NOD mice where disease develops more commonly in females. The incidence of diabetes in BB rats is not affected by gonadectomy or the administration of androgens as occurs with NOD mice. In contrast to humans and NOD mice, BB/Wor rats, the most commonly used substrain of BB rats, are severely lymphopenic. They have a marked decreased number of mature T lymphocytes in peripheral blood, spleen and lymph nodes. The CD4+ subset is substantially reduced but the CD8+ subset is almost completely absent. Natural killer cells are relatively over expressed. Several review papers have been published on this model

(Diabetes and Metabolism Reviews, 8: 9-37;1992).

BB rats were immunized with a combination of the anthrax and DTP vaccines (n=20) or nothing as a control (n=28). Groups contained approximately equal number of male and female rats. The vaccinated group was given the following dosing schedule: day 1 (.1ml,1:5); day 4 (.15ml, 1:5), day 11 (.15ml, 1:5), day 25 (.2ml, 1:5), day 39 (.2ml, 1:5), day 53 (.2ml, 1:5), day 61 (.2ml 1:2.5), and every 14 days for 3 more injections at approximately (.2ml, 1:2.5). Days of injection varied by one at times. The notation 1:5 means 1 part vaccine to 5 parts PBS. At 16 weeks of age 54% of the untreated rats had developed diabetes and or died compared to 20% in the vaccinated group. At 20 weeks of age 54% of the untreated rats had developed diabetes and or died compared to 25% in the vaccinated group. At 32 weeks the results were 54% versus 35% respectively (graph I) which represents a 34% reduction in the incidence of diabetes. The difference between the two groups were statistically significant at 20 weeks (P=0.027). The findings that the method of immunization can prevent diabetes in both NOD mice and BB rats provides strong proof that methods of immunization presented in the specification have the ability to prevent chronic immune mediated diseases in mammals with very different genetic defects.

MPEP §2107.02(d) states that "Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials." Nonetheless, Applicant has supplied human epidemiological data supporting his assertion of utility. This data revealed that standard childhood immunizations (i.e., later than when taught herein) against infectious disease increased the incidence of diabetes. It also indicated that early immunization with BCG and smallpox reduced the incidence of diabetes (although this effect was not recognized prior to the instant invention).

An epidemiology study described in example 101 of the specification showed that the incidence of diabetes in western European countries was closely correlated with a country's

vaccination schedule. Europe was chosen because in a relatively small geographic area there are many different countries that have different immunization schedules and the incidence of diabetes in the countries is known. The people in the western European countries have closely related racial backgrounds, diets, economic standards of living, and standards of health care. Eastern European countries of the former communist block were excluded because their standard of living and standard of medical care is not up to western levels.

The data correlating the incidence of diabetes to immunization schedule in western European countries is presented in Tables I-IV of this application.

The data in Tables I-IV discussed in Example 101, substantiates the experimental animal findings. According to Table I, administration of vaccines after 2 months increases the incidence of diabetes while administration of vaccines at birth can prevent diabetes. The findings are highly statistically significant. Administration of the pertussis vaccine after 2 month of age explains the higher incidence of diabetes in group 3 compared to most regions in group 1. Administration of the BCG vaccine after 2 months of age explains the higher incidence of diabetes in Group 4 compared to group 3. Administration of the Hemophilus influenza vaccine after 2 months of age explains the higher incidence of diabetes in group 5 compared to 4. The ability of the BCG vaccine to protect against diabetes when administered at birth explains the lower incidence of diabetes in group 2 compared to most regions in group 3.

Temporal studies (Table II-IV) were done to show the incidence of diabetes changed in a rational way after the immunization schedule changed. Published reports, showing that diabetes in humans can be caused by transient immune disturbances at birth, are also discussed in Example 101.

The epidemiological data presented above is evidence of efficacy in humans. In re Irons, 144 USPQ 351 (CCPA 1965)

held that "historical" data could be used to establish utility.

9.2. The Examiner has more recently questioned the extrapolation from rodents to humans "because of the criticality of the age of administration of the immunogens and the difference in maturation rates between rodents and humans" (OA §4(i)).

The issue of maturation rates is discussed in the specification. It is not the overall maturation rate which is important, just the rate of maturation of the immune system.

The specification states at page 27, lines 15-23:

> The immune systems of mice and men mature at comparable rates, with both species capable of mounting immune responses to vaccine antigens by the time the recipients are several months old. A comparison of the experimental and epidemiological examples in this specification supports this conclusion. Subtle differences in the rates of development of the immune systems of mice and humans may be detected however using a broad range of assays including in vivo assays, in vitro assays, in vitro assays and phenotypic cell assays.

It then discusses the appropriate assays in detail, at page 27, line 24 to page 29, line 12, and concludes at page 29, lines 13-19:

> The present invention therefore can include administration of the immunogens to humans when said humans' immune systems are in a state of maturation and responsiveness comparable to that of mice or rats at the times indicated above, in such circum-stances as it would be less effective to administer those immunogens to humans at the same chronological ages as they were administered to mice or rats.

In view of the issue raised by the Examiner, Applicants filed a supplemental amendment adding new claims which refer to first administration to a human subject when the immune system of that subject is at a state of maturation comparable

to that achieved prior to 42 days after birth in a mouse or rat.

On the issue of maturation, mice develop faster than humans. If we give a dose of vaccine before 42 days of age in mice, and it reduces the incidence or severity of diabetes, then giving the same vaccine at the same time to humans should also be effective, because, at the same age, the human will be at an even earlier stage of maturation than the mouse. In our examples, the day of first administration was day 8 in Example 1, day 1 in Example 2, day 10 in Example 3, day 1 in Example 4 (rate), and day 1 in Example 5. Even day 8 in the mouse will certainly correspond to a very young human.

Vertically transmitted viral infections appear to be associated with an increased risk of diabetes and other autoimmune disease. Mothers become infected with viruses such as the enterovirus and rubella virus when they are pregnant leading to an infection of the newborn and an increased risk of autoimmunity including IDDM later in life. Vertically transmitted viruses have been shown to induce diabetes in both mice and humans. For mice, see Gaskins, et al., J. Clin. Invest., 90:2220-7 (1992) (retrovirus in NOD mice); Suenaga and Brown, Diabetes, 37:1722 (1988) (abstract); Serreze, et al. Diabetes, 37:351-8 (1988). In humans, see Dahlquist, et al., Diabetes Care, 22:364-65 (1999) ("enterovirus RNA has been detected early in pregnancy in mothers of children who later become diabetic in a higher frequency than that found in mothers of control subjects")[14].

It has been shown that immunization of newborns with vaccines after birth can protect against vertical transmission of viruses such as hepatitis B. Administration of antiviral drugs after birth can prevent vertical transmission of the HIV

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[14] The discussion of HIV and CMV in the paragraph bridging pp. 9-10 of the October 27, 1999 response was not directed to the maturation rate issue considered here, but rather to issue X below. Hence, the Examiner's comments on page 7 of the March 13, 2000 communication are not apropos.

(AIDs) virus to newborns.

It is also known that administration of interferons will stop the replication and spread of viruses. It would be expected that giving an immune stimulant like a vaccine which cause interferon release would impede vertical transmission of viruses and thereby decrease the risk of IDDM.

Vertical transmission of viruses in NOD mice has also been implicated as a cause of diabetes in mice and would explain why early immunization is effective in these animals. Viral transmissions are similar in mice and men so the comparison of age is a moot point.

The Examiner did not seem to understand the issue of virus infection. Viruses replicate at the same rate in mice and humans. Early immunization causes interferon release which slows the replication of viruses, which otherwise increase the risk of diabetes.

10. (Issue IX) Is the specification enabling for the use of early immunization to immunize against an infectious disease as well as to reduce the incidence or severity of diabetes?

The Examiner has questioned the enablement of claims for immunization against an infectious disease, in particular, against HIV, HCV, and HSV. See October 2, 1998 office action, page 3, line 19 to page 5, line 12; page 6, lines 11-13; May 4, 1999 office action, sections 4(f) and (j).

A distinction must be drawn between those claims which recite reducing the incidence or severity of a chronic immune-mediated disorder, without reference to the effect on any infectious disease (claims 27, 32, 33) and those which contemplate that one or more of the immunogens is also protective against an infectious disease (claims 31, 36, 59). In the latter category, one must also distinguish between claims which are generic in character; and those which specify

particular immunogens/infectious diseases.

10.1. In section 4(f), the Examiner cites the intended use from the preamble of kit claim 59 ("for use to protect a mammal against an infectious disease). The Examiner completely ignores the very different preamble of claim 27 ("to reduce the incidence or severity of a chronic immune-mediated disorder"). While we agree that a particular immunogen may have both these effects, the application does not require that it be used to immunize against an infectious disease at all. Clearly, the "nonpediatric immunogens" of pp. 35-36 would be administered pediatrically in the United States principally to protect against juvenile diabetes, etc, and not against an infectious disease.

While there may be uncertainty as to the best age at which to vaccinate in order to elicit a specific, infectious disease-protective response to the immunogen in question, that is irrelevant to devising a vaccination schedule when the purpose is just to reduce the incidence or severity of an immune disorder. Method claims 32 and 33 and kit claim 27 do not require an effect against the infectious disease. Moreover, it is irrelevant to those claims whether the immunogen derived from HCV, HIV, etc. will protect against the infectious disease in question.

10.2. Claims 31 and 36, and new claim 59 (replacing claim 25) do recite protection against an infectious disease. However, these claims contemplate use of an immunogen known to protect against the infectious disease in question, and merely call for either an immunization schedule which reduces the risk of contracting a chronic immune-mediated disorder, or (in the case of claim 59) a warning that a particular schedule could increase that risk.

The prior art taught devising an immunization schedule for immunization against infectious diseases which (1) protected against the infectious disease, while (2) keeping side effects to tolerable levels. The side effects then recognized were, for example, soreness, fatigue, and vomiting,

acute allergic reactions, and contraction of the infectious disease (if not completely killed or attenuated). It was not recognized that immunization could also increase the incidence or severity of a chronic immune mediated-disorder, such as diabetes or SLE.

Based on applicants' teachings, those skilled in the art will evaluate the chronic immune adverse effects of various alternative immunization schedules, together with evaluating the acute and chronic protective immune response and the acute allergic response to the immunization.

As a result, an immunization schedule may be adopted which sacrifices some of the infection-preventive effect in return for a lower incidence or severity of chronic immune-mediated disorders, just as prior schedules have made similar compromises to reduce other side effects.

The data shows that doses routinely given to prevent infections alter the risk of chronic immune mediated disorders. it is generally known what doses alter infections for common immunogens, e.g., pertussis, diphtheria, tetanus, polio, measles, mumps, rubella, hepatitis B, hepatitis A, hemophilus, neisseria, pneumococcus, varicella etc. The person skilled in the art only needs to determine, without undue experimentation, a dose giving an effect, not an optimal dose.

Applicant would be willing to amend claims 31, 36 and 59 to recited that the method (31) and kit (36, 59) are for "eliciting an immune response in a mammal which recognizes an immunogen associated with an infectious disease to which said mammal is susceptible", without explicitly requiring an immunizing or protective effect. See claim 101, previously refused entry.

10.3. The question of coverage of future vaccines (4(j)) is one considered and resolved during the prosecution of the parent application, Serial No. 08/104,529, now USP 5,728,385. The Examiner of the parent application said that Applicant

could not specifically claim immunization against HIV, but could claim immunogens, implicitly including HIV, generically. That permitted a compromise, whereby Applicant received generic coverage of various immunogens, including HIV, but did not specifically claim HIV. The present Examiner would apparently limit Applicant only to those antigens already in use as vaccines.

That position is entirely without justification when the claimed purpose of the immunogen is merely to protect against diabetes. There was no known relationship between diabetes and anthrax, plague, diphtheria, pertussis or tetanus. Hence, the antidiabetic effect plainly was not a specific response, and hence there is no reason to believe that an HIV immunogen would not work just as well.

We need to remind the Examiner that the specification is presumptively enabling (In re Marzocchi), and that evidence of enablement (animal data, or human epidemiological data) must be rebutted by more relevant evidence of non-enablement in order to overcome that presumption. See MPEP § 2164.04, 2154.05, 2164.07.

The claims are written so that inoperative embodiments are automatically excluded (note the "acting" limitation), and see MPEP § 2164.08 (b). Applicant's discovery is of the general advantage of early immunization. It is not Applicant's job to identify every possible vaccine in order to enjoy generic protection of his discovery. If another scientist later identifies a protective immunogen for HSV, HCV, HIV or CMV, and administers it before 42 days after birth to reduce the incidence or severity of diabetes, then that later scientist is profiting from Dr. Classen's discovery, and should pay tribute to it.

With regard to the effect of administering viral proteins, all viral proteins can elicit an immune response. Some elicit a protective response, others do not. Whether the response is protective or not depends inter alia, on (1) are there several strains of the virus and, if so, is the protein

in question strain-specific, and (2) does the virus travel through the blood or by cell-to-cell direct contact.

With regard to HIV, CMV, and HSV in particular, immunogens are known for each. See Gringeri, et al., J. Hum. Virol. 1:293-8 (1998) (HIV-1 Tat protein); Lambert, et al., J. Acquir. Imm. Defic. Syndr. Hum. Retroviral., 1a:451-61 (1998) (HIV gp120, gp160); Limsuwan, et al., Vaccine, 16:142-9 (1998) (gp120 depleted inactivated vines HZ321); Straus, et al., J. Infect. Dis., 176:1129-34 (1997) (HSV type 2 gpD and gbB); Adler, et al., Pediatr. Infect. Dis. J., 17:200-6 (1998) (live attenuated CMV Townestrain), copies of abstracts enclosed previously.

11. (Issue X) Is the specification enabling for the use of early immunization to reduce the incidence or severity of a chronic immune-mediated disorder, in particular, of an autoimmune disease, other than diabetes?

The next issue relates to the inhibition of chronic immune mediated disorders other than diabetes. (OA of October 2, 1998, page 6, lines 2-3.)

The Examiner doubts the ability of a person of ordinary skill to adapt the teachings of the present invention to a chronic immune mediated disorder (as defined at pages 21-24 of the specification) other than diabetes.

It is well settled that the number of embodiments embraced by a claim is not the best measure of the difficulty of practicing it without undue experimentation. Disorders which are manifested through a common mechanism are likely to have a common cure or palliative. For example, a patient suffering from an allergic response may be given an antihistamine, regardless of the nature of the allergen. A particular immunosuppressant may be useful for treating a variety of autoimmune diseases.

11.1. Generally speaking, it is believed that people are

genetically predisposed to develop autoimmune diseases later in life. While the diseases are polygenic, at least some of the predispositive genes must affect multiple diseases, as it is not unusual for several members of the same family to manifest different autoimmune diseases, see Amer. J. Human Genet., 38:170-87 (1986) (Multiple diagnosis in the same individual is also not uncommon, see above). These phenomenon are in part explained by the link between certain high risk genes and the development of autoimmunity, in fact a single gene may be associated with an increased risk of several different autoimmune diseases, see above.

It is also believed that the autoimmune response is environmentally triggered, as it does not occur in all predisposed individuals. Both pathogens and xenobiotic substances have been identified as potential triggers; in some cases, the same agent has been identified as a trigger for more than one autoimmune disease, see Lancet, July 17, 1982 at page 159.

The different "diseases" are characterized based on which tissues are adversely affected, and how. Because the proximate cause is always an immune response, it is probable that one or more steps in the causal chain are common to all or most autoimmune diseases, implying that a common cure or palliative is feasible.

Therapeutic cytokines including interferons and interleukin 2 cause a significant number of recipients to develop autoimmune disease (see Physician Desk Reference). These cytokines are released naturally following the exposure to infectious agents and or vaccines.

Thus, a therapeutic intervention at the cytokine production or release stage could have a pervasive effect on autoimmune diseases.

Moreover, it is possible to use a "brute force" approach, such as administration of a nonspecific "anti-inflammatory" or "immunosuppressive agent." These are used in clinical treatment of autoimmune diseases today (see PDR). The use of

these agents indicates that the diseases treated do have at least in part a common mechanism.

Applicant has postulated, in his specification, that interferons modulate diabetes, and that the administration of immunogens affect interference release by a non-immunogen specific mechanism, as previously discussed in this Appeal Brief at pp. 31-33.

11.2. Many patents have been issued which claim treatment of a large class of diseases while only showing examples of treating a single disease. In the field of autoimmune diseases, the following patents come to mind:

i) U.S. patent 4,695,459 claim 3 (column 6 line 45) claims a method of treating multiple diseases in humans including multiple sclerosis, systemic lupus erythematosus, psoriasis, juvenile onset diabetes, Sjorgren's disease, thyroid disease, or myasthenia gravis. (These are chronic immune-mediated disorders). The specification only gave an example of treating EAE in mice.

ii) U.S. patent 4,710,380 claim 1 (column 5 line 47) claims a method of treating human or mammal subjects for "disorders characterized by an hyperactive immune response". The term is similar to the term chronic immune mediated disorders used in our application because both encompasses rheumatoid arthritis, lupus, type I diabetes, and other autoimmune disorders (page 36 line 8). Patent 4, 710,380 contains only examples of rheumatoid arthritis patients being treated with its claimed method, however, its claim 1 encompasses all hyperactive immune responses.

11.3. In paragraph 4 of the Classen Declaration filed March 25, 1999, data is presented which shows that the method of the present invention inhibits spontaneous autoimmunity in MRL/1pr mice. These mice, absent intervention, develop a disease which closely resembles the autoimmune disorder Systemic Lupus Erythematosus (SLE) in humans. Like SLE patients, the MRL/1Pr mice develop anti-DNA and anti-nuclear autoantibodies which can form immune complexes, which in turn

can cause arthritis, dermatitis, and glomerulonephritis.

The MRL data is important not only because it is a good model for human SLE but because this autoimmune disease is both genetically, immunologically, and clinically very different from diabetes. Appendix 1 to the March 25, 1999 amendment summarizes a few references verifying both the similarity of the disease in MRL mice to SLE in humans and the clinical importance of the MRL model.

As described in the declaration, MRL/MpJ-lpr mice were injected either with a control (PBS) or with the anthrax/DTP combination, following an immunization schedule within the teachings of the present invention. At 15 weeks, 26.3% control mice exhibited significant proteinuria (an accepted sign of glomerulonephritis), while only 7.7% of the vaccinated mice developed comparable levels of protein in their urine.

This data of course supports extending coverage from diabetes to SLE. However, because SLE and diabetes are so different, it also lends support to generic coverage of chronic immune-mediated disorders, or at least of autoimmune diseases.

Diabetes and SLE are quite different autoimmune diseases. Diabetes results from immune destruction of specific cells, the islet cells, which are present in the pancrease. The pathogenesis involves both antibodies and cytotoxic T cells. SLE does not involve the destruction of a specific cell type. Instead the autoimmune disease is against soluble antigens or antigens that are not cell specific such as DNA.

12. (Issue XI) Is the specification enabling for determining the effect of immunization schedules on the incidence or severity of immune disorders?

Finally, the Examiner refers to the alleged difficulties "calculating what dosage, method of administration, and frequency of administration" will "substantially induce an immune disorder" (see claim 2). It is, of course, as easy to

determine whether an immunization schedule substantially induces a disorder as to determine whether it inhibits it. The test is the same; they are two sides of the same coin.

With regard to the issue of the determination of an effective immunization schedule, the PTO appears to have exaggerated the difficulty of this task. Applicants wish to call the Examiner's attention to the following considerations:

(a) it is routine in the art to conduct initial efficacy studies in mice and rats and to then scale-up to humans. This requires adjustment for differences in body weight, metabolism, development, etc. Such adjustments must now be deemed routine.

(b) immunization schedules are specifically suggested at pages 24-33 of the specification.

(c) dosages are discussed at pages 47-51 of the specification, and safe dosages are known for many of the contemplated immunogens. The epidemiology data indicates that the same doses given to prevent infections are also altering the risk of diabetes, therefor extensive testing to find the appropriate dose is not necessary.

(d) the human immunization schedules which resulted in favorable epidemiological effects on diabetes are known (see, e.g., table I, referring to vaccination with BCG at birth in 1988 in Ireland, France and Austria). Those dosages of other immunogens, such as pertussis, which, upon late administration, increased the incidence of diabetes are also known and presumably would still modulate diabetes (although more favorably) if given earlier.

The principal parameters of the immunization schedule are the timing of the first dose, the total number of doses, and the interval between doses.

The initial dosing date is addressed at page 25, lines 17-27; the total number of doses at page 25, line 28 to page 26, line 17, and the interval at page 26, line 18 to page 27, line 6. The interplay of these factors, as they affect the total number of doses within a given period, is discussed at page 27, lines 7-14.

Four specific immunization schedules are set forth in Table 5 and discussed at page 29, line 20 to page 30, line 30.

These schedule can be characterized as follows:

Schedule	Dose, Initial	Doses, Total	Interval
1	w0	10	2w
2	w2	9	2w
3	w0	7	3w
4	w0	8	2wx3 3wx4

Note that schedule 4 is not entirely regular, but conforms to the practice discussed at page 26, lines 22-25.

The schedules in the Examples were

Schedule	Initial	Total	Interval
Ex. 1	8d	3	7dx1 14dx1
Ex. 2	1d	9	irregular (2d-2w)
Ex. 4	1d	10	irregular (3d-2w)

One skilled in the art would know the limitations of immunizing humans and would be able to design an vaccination schedule to perform the intended function. The frequency of immunization is limited by the frequency that individuals are willing to have a health official vaccinate their children. In Belgium in the 1960s, well baby care involved bringing the child to the doctor every 2 weeks until the child was 8 weeks old J. Royal College of General Practitioners 24:676-686, 1974).

It is respectfully urged that with the guidance of the recommendations and examples in the specification, a person of ordinary skill in the art can develop a safe and effective immunization schedule without undue experimentation. This conclusion is confirmed by paragraph 6 of the Classen Declaration.

In general, the response is expected to be increased by

administering the immunogen earlier, more often, at shorter intervals, and at higher doses. Therefore, if a preferred schedule is tried, and found less than optimal, one or more of the schedule parameters would be changed, i.e., starting earlier, giving more doses, reducing the dose interval, or increasing the size of each dose (or at least of the first dose). If the anti-diabetic response is satisfactory, but the anti-infectious disease effect (if sought), is unsatisfactory, the first dose may be given somewhat later. The practitioner may also wish to reduce the number of doses for economic reasons, or increase the time interval for the sake of patient convenience.

The systematic variation of a small number of quantifiable treatment parameters, so as to optimize the subject's response, is the very essence of routine practice.

With regard to the route of administration, several options are set forth on page 52. For each of the conventional pediatric immunogens, one or more accepted routes exist, and these would be used unless problems (not presently expected) are encountered. Most human vaccines are given intramuscularly.

Respectfully submitted,

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APPENDIX

5. The Kit of claim 59 wherein one immunogen other than a BCG, diphtheria, tetanus, pertussis, polio, hepatitis A, hepatitis B, hemophilus influenza, measles, mumps and rubella, influenza, cholera, plague, pneumoccccus, neisseria, varicella, rabies, typhoid and yellow fever immunogen is provided.

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6. The method of claim 32, wherein for at least one such immunogen, the total dosage during the first 112 days after birth is substantially greater than that required for immunization against the infectious disease with which it is associated.

8 (amended). The [method] kit of claim [31] 59 wherein, following such instructions, the first administration is when the mammal is less than 28 days old.

10 (amended). The [method] kit of claim [21] 59 wherein, following such instructions, the shortest interval between two successive dosings of at least one immunogen is les than 28 days.

11 (amended). The [use] kit of claim [21] 59 wherein, following such instructions, during the first 175 days from birth the longest interval between two successive dosings of at least one immunogen is less than 28 days.

15. A Kit of claim 27, wherein said chronic immune mediated disorder is a non-streptozotocin-induced diabetes mellitus.

16 (amended). The [method] kit of claim [31] 59 wherein, following such instructions, said mammal is a human.

19. An immunogenic agent comprising a pediatric immunogen and a non-pediatric immunogen, wherein the non-pediatric immunogen is selected from the group consisting of anthrax, plague, encephalitis, meningococcal, meningitis, pneumococcus, pneumonia, typhus, typhoid fever, streptococcus, staphylococcus, neisseria, lyme disease, cholera, E. coli, shigella, leishmania, leprosy, cytomegalovirus (CMV), respiratory syncytial virus, Epstein Barr virus, herpes, influenza, parainfluenza, rotavirus, adenovirus, human immunodeficiency virus (HIV), hepatitis A, NonA NonB hepatitis, varicella, rabies, yellow fever, rabies, Japanese encephalitis, flavivirus, dengue toxoplasmosis, coccidiomycosis, schistosomiasis, and malaria immunogens and a molecule that cross reacts immunologically to at least one of said immunogens.

26. The kit of claim 27 wherein said instructions state that the kit is to be used to reduce the incidence or severity of diabetes.

27. A kit for use, prophylactically or therapeutically, to reduce the incidence or severity of a chronic immune mediated disorder, said kit comprising one or more containers, each container holding one or more pharmaceutically acceptable doses of one or more immunogens, said kit further comprising labeling indicating that the kit can be used to reduce the incidence or severity of a chronic immune-mediated disorder in a mammal, and instructions for the prophylactic or therapeutic use of said immunogens to reduce the incidence or severity of a chronic

immune-mediated disorder in a mammal to which one or more doses of said immunogens are administered according to an immunization schedule set forth in said instructions, said immunogens, when so administered, acting to substantially reduce the incidence or severity of said chronic immune-mediated disorder, wherein said schedule, according to said instructions, calls for the first dose of an immunogen to be given before 42 days after birth.

28. The Kit of claim 27 where if the disorder is diabetes, the diabetes was not streptozotocin-induced.

29. The Kit of claim 27 wherein at least one immunogen other than a pertussis immunogen is administered.

30. The Kit of claim 59 wherein said Kit contains at least one immunogen selected from the group consisting of a diphtheria, tetanus, polio, Hepatitis B, Hemophilus influenza b, pertussis, and BCG immunogen.

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32 (amended). A method of reducing the incidence or severity of [an] a chronic immune-mediated disorder in a mammal which comprises administering to said mammal one or more immunogens, according to an immunization schedule by virtue of which the mammal receives, at , one or more pharmaceutically acceptable doses of said immunogens, said administrations resulting in an immune response in said mammal which substantially reduces the incidence or severity of at least one chronic immune-mediated disorder in the mammal,

the first dose of said immunization schedule being administered when the mammal is less than 42 days old, measured from birth,

where, if only one immunogen is administered according to said immunization schedule, that immunogen is one other than BCG, and, if said one immunogen is whole cell pertussis, the schedule is one other than a schedule of three doses at one week intervals, all given in the first month,

where, when all of the immunogens administered are selected from the group consisting of BCG, diphtheria, tetanus, whole cell pertussis, polio, hepatitis B, hemophilus influenza, measles, mumps and rubella immunogens, at least one of the following conditions applies: (a) one or more immunogens are administered on at least three different dates prior to 42 days after birth, or (b) one or more immunogens are administered on at least three different dates, and the maximum interval between administrations is about two weeks, or less.

33. A method of reducing the incidence or severity of an immune disorder in a mammal which comprises administering to said mammal one or more immunogens, according to an immunization schedule by virtue of which the mammal receives, at specific times after birth, one or more pharmaceutically acceptable doses

of said immunogens, said administrations resulting in an immune response in said mammal which substantially reduces the incidence or severity of at least one chronic immune-mediated disorder in the mammal, the first dose of said immunization schedule being administered when the mammal is less than 42 days old, measured from birth,
where said immunogens are administered from a kit according to claim 27.

34. The kit of claim 27, where said kit is to be used to reduce the incidence or severity of an autoimmune disease, and said labeling so indicates and provides instruction for such use.

35. The kit of claim 27 wherein said labeling states that said kit is to be used to reduce the incidence or severity of systemic lupus erythrematosis, and provides instruction for such use.

36. The kit of claim 27, at least one of said immunogens also acting to substantially reduce the incidence or severity of an infectious disease to which said mammal is susceptible, and said labeling so indicates, and provides instruction for such use.

37. The kit of claim 27, which includes at least one immunogen other than a BCG, diphtheria, tetanus, pertussis, polio, hepatitis A, hepatitis B, hemophilus influenza, measles, mumps and rubella, influenza, cholera, BCG, plague, pneumococcus, neisseria, varicella, rabies, typhoid and yellow fever immunogen is administered.

38. The kit of claim 59, wherein, according to said instructions, for at least one such immunogen which elicits an immune response to one of said infectious diseases, the total dosage during the first 112 days after birth is substantially greater than that required for immunization against the infectious disease with which it is associated.

39. The kit of claim 27, wherein, according to said instructions, the first administration when the mammal is less than 28 days old.

40. The kit of claim 27 wherein according to said instructions at least one immunogen is given in two or more dosings such that the shortest interval between two successive dosings thereof is less than 28 days.

41. The kit of claim 27, wherein according to said instructions at least one immunogen is given in two or more dosings such that the longest interval between two successive dosings thereof is less than 28 days.

43. The kit of claim 27 where the mammal is human.

44. The kit of claim 43 where said kit contains a killed vaccine.

46. The kit of claim 43 where said kit contains a live vaccine.

48. The Kit of claim 27 in which the mammal is an animal model of diabetes or systemic lupus erythematosus.

49. The kit of claim 59 where said labeling indicates that starting the first dose of immunization after 56 days after birth may not reduce said chronic immune mediated disorder or may increase the risk of said chronic immune mediated disorder.

50 (amended). The [method] kit of claim [8] 27 wherein, following such instructions, the first administration is when the mammal is less than 14 days old.

51 (amended). The [method] kit of claim [8] 27 wherein, following such instructions, the first administration is when the mammal is about 7 days old.

52 (amended). The [method] kit of claim [11] 27 wherein, following such instructions, the longest interval between two successive dosings is less than or about 14 days.

55. The kit of claim 59 in which at least one immunogen is a hemophilus influenza immunogen.

--56. A method of reducing the incidence or severity of an immune disorder in a mammal which comprises administering to said mammal one or more immunogens, according to an immunization schedule by virtue of which the mammal receives, at , one or more pharmaceutically acceptable doses of said immunogens, said administrations resulting in an immune response in said mammal which substantially reduces the incidence or severity of at least one chronic immune-mediated disorder in the mammal,

the first dose of said immunization schedule being administered when the mammal is less than 42 days old, measured from birth,

where, if only one immunogen is administered according to

OIPE JC68 MAY 01 2000 PATENT & TRADEMARK OFFICE

said immunization schedule, that immunogen is one other than BCG, where, when all of the immunogens administered are selected from the group consisting of BCG, diphtheria, tetanus, whole cell pertussis, polio, hepatitis B, hemophilus influenza, measles, mumps and rubella immunogens, at least one of the following conditions applies: (a) one or more immunogens are administered on at least three different dates prior to 42 days after birth, or (b) one or more immunogens are administered on at least three different dates, and the maximum interval between administrations is about two weeks, or less, and
where one or more immunogens are administered on at least four different dates.

57. The method of claim 56 where one or more immunogens are administered on at least four different dates during the first 112 days after birth.

58. The method of claim 56 where one or more immunogens are administered on at least four different dates during the first 42 days after birth.

59. A kit for use to protect a mammal against an infectious disease to which a mammal is susceptible, said kit comprising one or more containers, each container holding one or more pharmaceutically acceptable doses of one or more immunogens, at least one of said immunogens acting to protect against said infectious disease when appropriately administered to said subject,
said kit comprising labeling indicating

(a) that the kit can be used to reduce the incidence or severity of a chronic immune-mediated disorder in a mammal, and providing instructions for the prophylactic or therapeutic use of said immunogens to reduce the incidence or severity of a chronic immune-mediated disorder in a mammal, said instructions stating that one or more doses should be administered according to an immunization

schedule set forth in said instructions, said immunogens, when so administered, acting to substantially reduce the incidence or severity of said chronic immune-mediated disorder,

or

(b) that the kit, depending on when one or more of said immunogens is administered, may, can or does increase the incidence or accelerate the onset of a chronic immune-mediated disorder.

60. The kit of claim 59 where (a) applies.

61. The kit of claim 59 where (b) applies.

62. The kit of claim 61, said labeling further comprising instructions for administering such immunogens so as to avoid such increase in the incidence or severity, or such acceleration in the onset, of said chronic immune-mediated disorder.

63. The kit of claim 59 wherein following such instructions the first administration is when the mammal is less than 14 days old.

64. The kit of claim 59 wherein following such instructions the first administration is when the mammal is about 7 days old.

65. The kit of claim 59 wherein following such instructions the longest interval between two successive dosings is less than or about 14 days.

66. The kit of claim 27 where at least one of said immunogens is a pediatric immunogen.

67. The kit of claim 66 where said pediatric immunogen is selected from the group consisting of BCG, measles, mumps, rubella, diphtheria, pertussis, hemophilus influenza, tetanus, hepatitis B, and polio immunogens.

68. The kit of claim 27 where at least one of said immunogens is a nonpediatric immunogen.

69. The kit of claim 68 in which said nonpediatric immunogen is selected from the group consisting of anthrax,

plague, encephalitis, meningococcal, pneumococcus, typhus, typhoid fever, streptococcus, staphylococcus, neisseria, lyme disease, cholera, E. coli, shigella, leishmania, leprosy, cytomegalovirus (CMV), respiratory syncytial, virus, Epstein Barr virus, herpes, influenza, parainfluenza, rotavirus, adenovirus, human immunodeficiency virus (HIV), hepatitis A, NonA NonB hepatitis, varicella, rabies, yellow fever, rabies, Japanese encephalitis, flavivirus, dengue, toxoplasmosis, coccidiomycosis, schistosomiasis, and malaria immunogens.

70. The kit of claim 27 in which at least one immunogen is selected from the group consisting of BCG, measles, mumps, rubella, diphtheria pertussis, hemophilus influenza, tetanus, hepatitis B, polio immunogens, anthrax, plague, encephalitis, meningococcal, meningitis, pneumococcus, pneumonia, typhus, typhoid fever, streptococcus, staphylococcus, neisseria, lyme disease, cholera, E. coli, shigella, leishmania, leprosy, cytomegalovirus (CMV), respiratory syncytial, virus, Epstein Barr virus, herpes, influenza, parainfluenza, rotavirus, adenovirus, human immunodeficiency virus (HIV), hepatitis A, NonA NonB hepatitis, varicella, rabies, yellow fever, rabies, Japanese encephalitis, flavivirus, dengue toxoplasmosis, coccidiomycosis, schistosomiasis, and malaria immunogens.

71. The kit of claim 27 in which at least one immunogen is selected from the group consisting of anthrax, plague, tetanus, pertussis, diphtheria, BCG, hemophilus influenza or smallpox immunogen.

72. The kit of claim 59 where at least one of said immunogens is a pediatric immunogen.

73. The kit of claim 72 where said pediatric immunogen is selected from the group consisting of BCG, measles, mumps, rubella, diphtheria, pertussis, hemophilus influenza, tetanus, hepatitis B, and polio immunogens.

74. The kit of claim 59 where at least one of said

immunogens is a nonpediatric immunogen.

75. The kit of claim 74 wherein said nonpediatric immunogen is selected from the group consisting of anthrax, plague, encephalitis, meningococcal, pneumococcus, typhus, typhoid fever, streptococcus, staphylococcus, neisseria, lyme disease, cholera, E. coli, shigella, leishmania, leprosy, cytomegalovirus (CMV), respiratory syncytial, virus, Epstein Barr virus, herpes, influenza, parainfluenza, rotavirus, adenovirus, human immunodeficiency virus (HIV), hepatitis A, NonA NonB hepatitis, varicella, rabies, yellow fever, rabies, Japanese encephalitis, flavivirus, dengue, toxoplasmosis, coccidiomycosis, schistosomiasis, and malaria immunogens.

76. The kit of claim 59 in which at least one immunogen is selected from the group consisting of BCG, measles, mumps, rubella, diphtheria pertussis, hemophilus influenza, tetanus, hepatitis B, polio immunogens, anthrax, plague, encephalitis, meningococcal, meningitis, pneumococcus, pneumonia, typhus, typhoid fever, streptococcus, staphylococcus, neisseria, lyme disease, cholera, E. coli, shigella, leishmania, leprosy, cytomegalovirus (CMV), respiratory syncytial, virus, Epstein Barr virus, herpes, influenza, parainfluenza, rotavirus, adenovirus, human immunodeficiency virus (HIV), hepatitis A, NonA NonB hepatitis, varicella, rabies, yellow fever, rabies, Japanese encephalitis, flavivirus, dengue toxoplasmosis, coccidiomycosis, schistosomiasis, and malaria immunogens.

77. The kit of claim 59 wherein at least one immunogen is selected from the group consisting of anthrax, plague, tetanus, pertussis, diphtheria, BCG, hemophilus influenza or smallpox immunogen.

78. The kit of claim 59 in which the disorder is an immune mediated cancer.

79. The kit of claim 59 in which the disorder is an autoimmune disease.

80. The kit of claim 79 in which the disease is a rheumatic disease or connective tissue disease.

81. The kit of claim 59 in which the disorder is a neurological disease.

82. The kit of claim 81 in which the disease is multiple sclerosis.

83. The kit of claim 59 in which the disorder is a chronic asthma or chronic allergy.

84. The kit of claim 59 in which the disorder is non-streptozotocin-induced diabetes.

85. The kit of claim 59 in which the disorder is systemic lupus erythematosis.

86. The kit of claim 59, said kit further comprising instructions for the use of an immunosuppressant to reduce the incidence or severity of chronic immune mediated disorder which might occur as a result of said administration of said immunogens in the absence of said immunosuppressant.

87. The kit of claim 59 which comprises said immunosuppressant.

88. The kit of claim 86 where said immunosuppressant is a glucocorticoid or a substance which induces the release of a glucocorticoid hormone.

89. The kit of claim 59 wherein none of the immunogens are adjuvanted with an aluminum salt or with another adjuvant whose ability to activate macrophage is about the same as or greater than that of an aluminum salt.

90. The kit of claim 59 in which the disorder is one which develops at least one year after a vaccination.

91. The kit of claim 59 wherein at least one immunogen is a viral immunogen.

92. The kit of claim 59 wherein at least one immunogen is a bacterial immunogen.

93. The kit of claim 59 wherein at least one immunogen is

a yeast, mold or plant immunogen.

94. The kit of claim 59 wherein at least one immunogen is an insect immunogen.

95. The kit of claim 59 wherein at least one immunogen is an immunogen of an allogeneic or xenogeneic animal.

96. The kit of claim 61 wherein the labeling indicates that the kit, depending on when one or more of said immunogens is administered, can or does increase the incidence or accelerate the onset of said disorder.

97. The kit of claim 61 wherein the labeling indicates that the kit, depending on when one or more of said immunogens is administered, may, can or does increase the incidence of said disorder.

98. The kit of claim 59 which includes at least one immunogen other than a pertussis immunogen.

99. The kit of claim 59 which includes at least one immunogen other than a BCG immunogen.

100. The kit of claim 59 where both (a) and (b) apply.

101. The method of claim 32 where at least one of said immunogens elicits an immune response in said mammal which recognizes an immunogen associated with an infectious disease to which said mammal is susceptible.--